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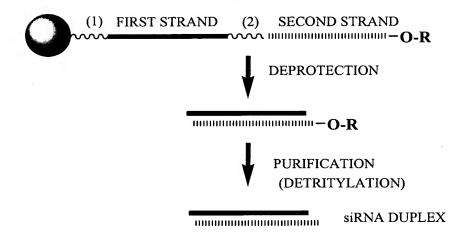
RNA Interference Mediated Treatment of Alzheimer's

Disease Using Short Interfering Nucleic Acid (siNA)

Serial No. TBA; MBHB02-728-B (400/120)

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Figure 1



= SOLID SUPPORT

R = TERMINAL PROTECTING GROUP FOR EXAMPLE: DIMETHOXYTRITYL (DMT)

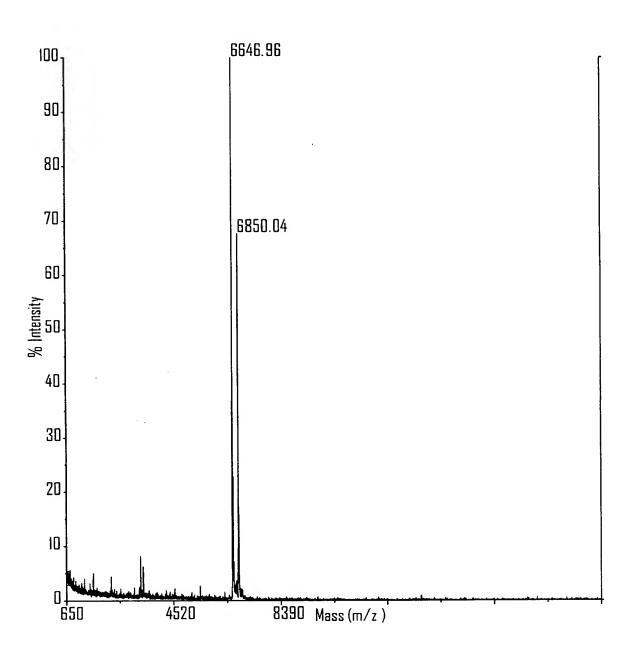
(1) = CLEAVABLE LINKER
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR
(2) INVERTED DEOXYABASIC SUCCINATE)

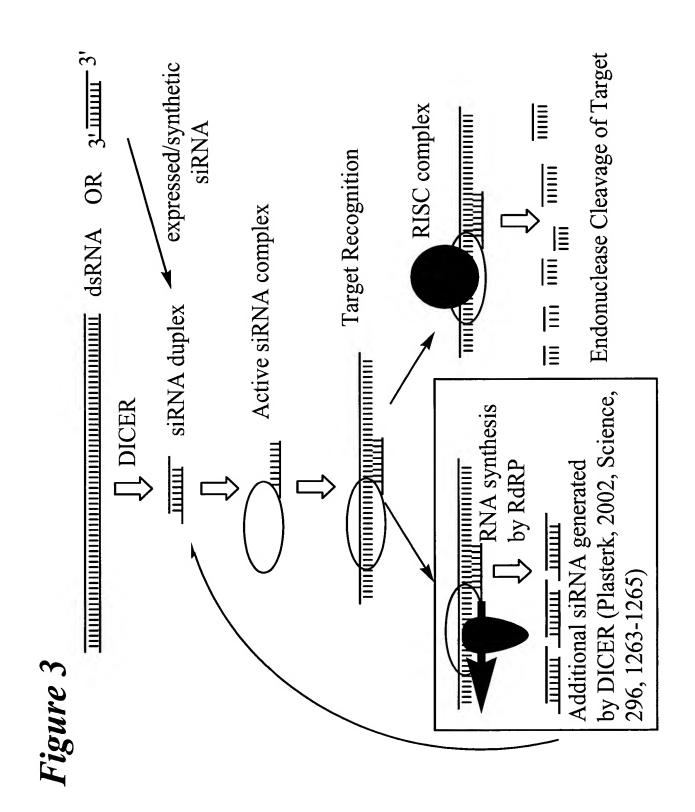
= CLEAVABLE LINKER (FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

INVERTED DEOXYABASIC SUCCINATE LINKAGE

GLYCERYL SUCCINATE LINKAGE

Figure 2





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Liama 1

	rigure 4	
	SENSE STRAND (SEQ ID NO 691) ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N)	1
A	5'- B-NNNNNNNNNNNNNNNNNNNNNNNNN -3'	
	$\int 3' - L - (N_s N) NNNNNNNNNNNNNNNNNNN -5'$	7
	ANTISENSE STRAND (SEQ ID NO 692) ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N)	
	SENSE STRAND (SEQ ID NO 693) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-OM EXCEPT POSITIONS (N N)	1
	$5'$ - NNNNNNNNNNNNNNNNNNN (N_s N) -3'	
${f B}$	$\begin{cases} 3'- L-(N_sN)NNNNNNNNNNNNNNNN -5' \end{cases}$	۲
	ANTISENSE STRAND (SEQ ID NO 694) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N)	
C	SENSE STRAND (SEQ ID NO 695)	l
	ALL PYRIMIDINES = 2'-O-ME OR 2'-FLUORO EXCEPT POSITIONS (N N)	
	$\int 5'$ - B-NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	٧
	$3'$ - L- (N_sN) N N N N N N N N N N N N N N N N N N	
	ANTISENSE STRAND (SEQ ID NO 696) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N)	
D	SENSE STRAND (SEQ ID NO 697) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY	
	5'- B-NNNNNNNNNNNNNNNNNNNNNNNN -3'	
	$3'$ - L- (N_sN) NNNNNNNNNNNNNNNNNNNNN -5' $($	_
	ANTISENSE STRAND (SEQ ID NO 694) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N)	
	SENSE STRAND (SEQ ID NO 698) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N)	
	5'- B-NNNNNNNNNNNNNNNNNNNNNNNN (NN)-B -3'	
\mathbf{E}	$\left. \left. \left\langle 3' \right\rangle \right\rangle - L - \left(N_{S} N \right) N N N N N N N N N N N N N N N N N $	-
	ANTISENSE STRAND (SEQ ID NO 694) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N)	
	CENICE CTRAND (CEO ID NO 407)	
	SENSE STRAND (SEQ ID NO 697) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY	
F	∫ 5'- B-NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	
L'	$3'$ - L- (N_sN) NNNNNNNNNNNNNNNNNNNN -5'	
	ANTISENSE STRAND (SEQ ID NO 699) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY	
	POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIC)

ES (eg. THYMIDINE) OR UNIVERSAL BASES

- B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENT
- L = GLYCERYL MOIETY THAT IS OPTIONALLY PRESENT
- S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE

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Figure 5

	rig	rure 3	
		SENSE STRAND (SEQ ID NO 700)	
A	5'-	iB-C A U G G C U G C C A U C U G C G C C T T-iB	-3'
A	خ کا ا	L-T _S T GUACCGACGGUAGACGCGG	-5'
		ANTISENSE STRAND (SEQ ID NO 701)	
	}	SENSE STRAND (SEQ ID NO 702)	\downarrow
-	5'-	c <u>a</u> uggcugcc <u>a</u> ucugcgccTT	-3'
B	₹ 3'-	L - T_ST g u \underline{a} c c g \underline{a} c g g u \underline{a} g \underline{a} c g g	-5' >
		ANTISENSE STRAND (SEQ ID NO 703)	
	}	SENSE STRAND (SEQ ID NO 704)	$\left\{ \right.$
	5'-	iB-cAuGGcuGccAucuGcGccTT-iB	-3'
\mathbf{C}	⊰ 3'-	L-T _S T G u A c c G A c G G u A G A c G c G G	-5'
		ANTISENSE STRAND (SEQ ID NO 705)	
	_		}
		SENSE STRAND (SEQ ID NO 706)	
n	5'-	iB-cAuGGcuGccAucuGcGccTT-iB	-3'
D	3'-	L - T_ST g u \underline{a} c c g \underline{a} c g g u \underline{a} g \underline{a} c g c g g	-5'
		ANTISENSE STRAND (SEQ ID NO 703)	
		SENSE STRAND (SEQ ID NO 707)	1
_	5'-	iB-cAuGGcuGccAucuGcGccTT-iB	-3'
\mathbf{E}	₹ 3'-	$L-T_STgu\underline{a}ccg\underline{a}cggu\underline{a}g\underline{a}cgcgg$	-5' }
		ANTISENSE STRAND (SEQ ID NO 703)	
	}	SENSE STRAND (SEQ ID NO 706)	$\left\{ \right.$
	5'-	iB-cAuGGcuGccAucuGcGccTT-iB	-3'
F	₹ 3'-	L-T _S T Gu A c c G A c G G u A G A c G c G G	-5' }
		ANTISENSE STRAND (SEQ ID NO 708)	
	L		J

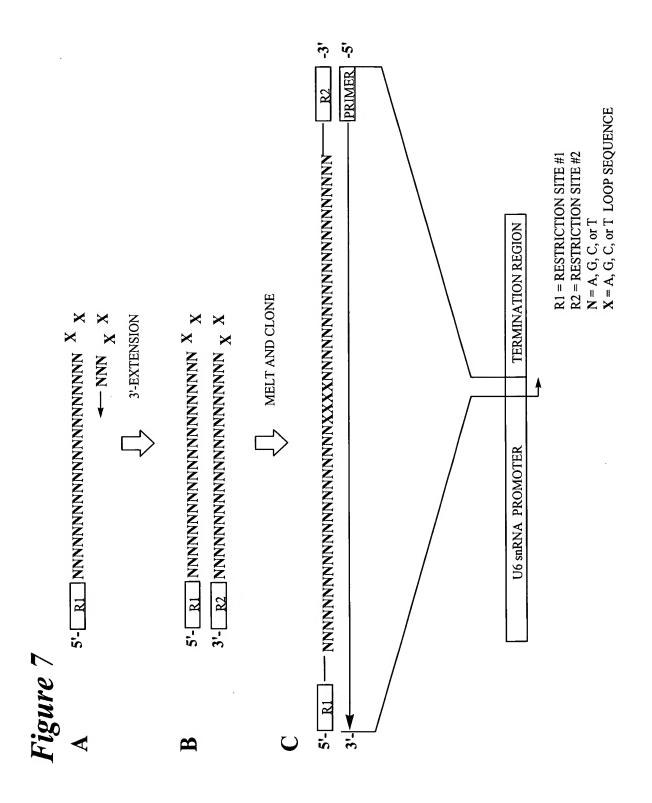
lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro italic lower case = 2'-deoxy-2'-fluoro underline = 2'-O-methyl

ITALIC UPPER CASE = DEOXY
B = INVERTED DEOXYABASIC
L = GLYCERYL MOIETY OPTIONALLY PRESENT
S = PHOSPHOROTHIOATE OR
PHOSPHORODITHIOATE

ANTISENSE ANTISENSE ANTISENSE ANTISENSE SENSE SENSE RNAi Z RNAi ANTISENSE 5' ANTISENSE ANTISENSE ANTISENSE SENSE SENSE SENSE 7

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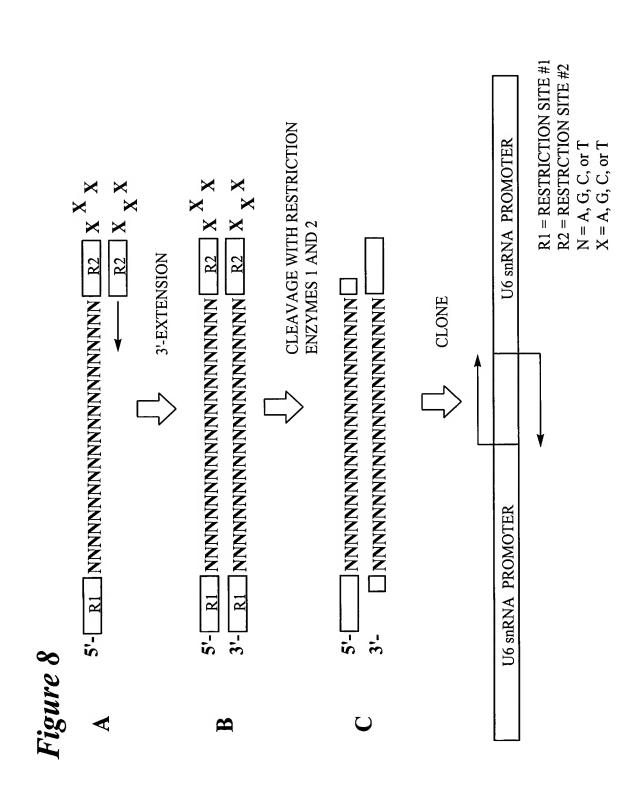
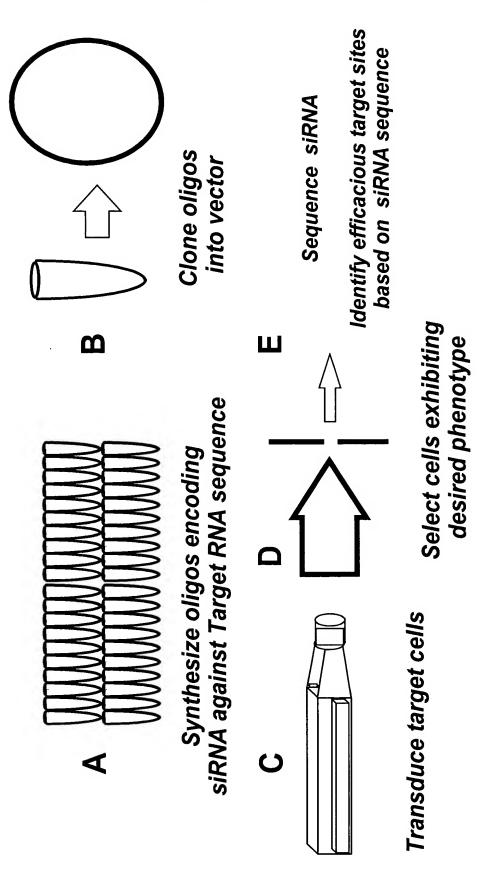


Figure 9: Target site Selection using siRNA



9 CH₃O S თ Figure 10 ک کی

R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl
B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

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Figure 11: Modification Strategy

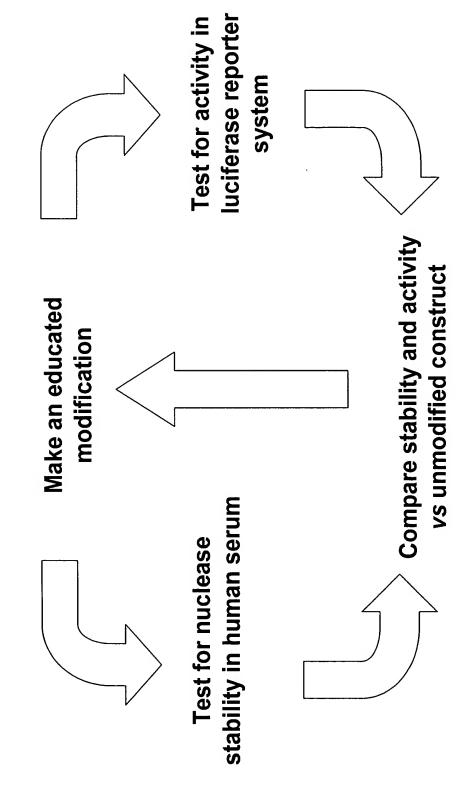


Figure 12: A549 24h BACE mRNA Expression

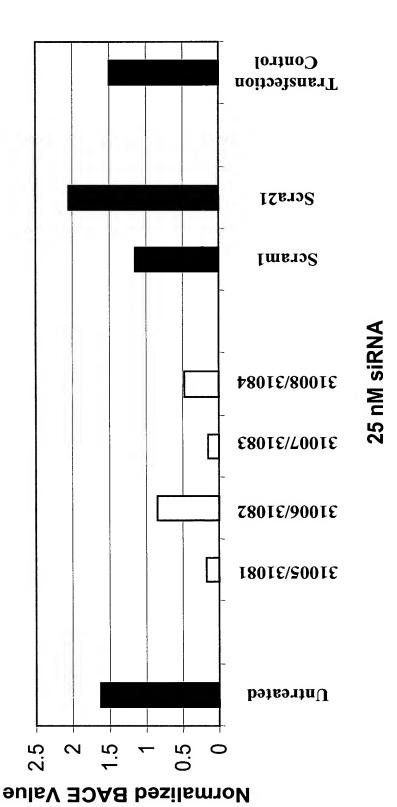
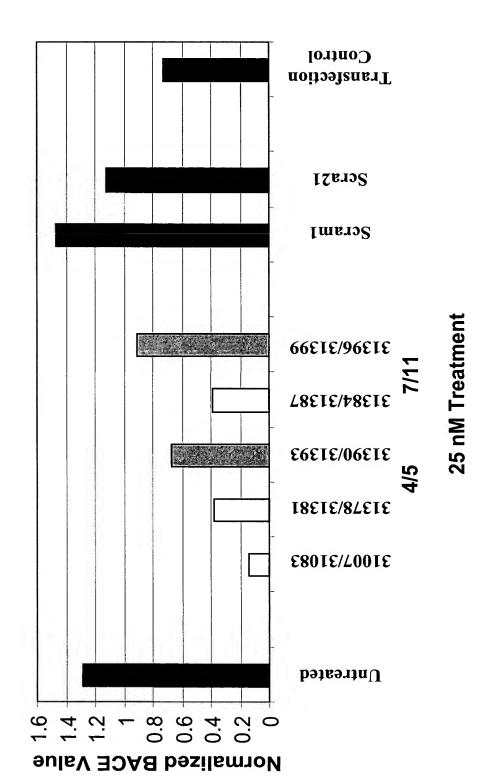


Figure 13: A549 24h BACE mRNA Expression using modified siNA



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